ORIGINAL RESEARCH

Tenofovir induced oral hyperpigmentation among HIV patients in Kodagu Karnataka: A clinico epidemiological study

[1]Dr. Deepa Venkatesh, [2]Dr. Dhyan Kushalappa P B, [3]Dr. Sagar Gopalakrishna, [4]Dr. Khwairakpam Chaoton Singh

[1]Associate Professor, Department of Dentistry, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India
[2]Assistant Professor, Department of Dentistry, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India
[3]Junior Resident, Department of Dentistry, Kodagu Institute of Medical Sciences,Madikeri, Karnataka, India
[4]Consultant Oral and Maxillofacial Surgeon, Imphal, Manipur, India

Corresponding Author
Dr. Deepa Venkatesh
Associate Professor, Department of Dentistry, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India

Received: 02Sept, 2023 Accepted: 25Sept, 2023

ABSTRACT

Objective: To assess the prevalence of Tenofovir induced oral hyperpigmentation among HIV-infected patients in Kodagu Karnataka.

Methods:168 HIV infected individuals who were receiving Tenofovir were included in the study. Proper muco-cutaneous examination was done. Site, duration from when the pigmented lesions started to appear and duration from when treatment was started were taken into consideration. All the collected data were recorded and statistically analyzed.

Results:A total of 168HIV infected patients on anti-retro viral therapy Tenofovir, Lamivudine and Efavirenz regimen were included in the study. Oral mucosal pigmentation was seen in 52 (31%) subjects and 6 (3.6%) subjects had both intra oral and extra oral pigmentation i.e. pigmentation of skin, nail and oral cavity.Majority of the study population 85 (50.8%) were on Tenofovir for more than 5 years.

Conclusion: Oral hyperpigmentation is one of the major side effect with prolonged treatment of Tenofovir. On prior explanation regarding adverse reactions adherence to the antiviral drug regimen can be improved.

Key words: Anti retro viral therapy, pigmentation, tenofovir-induced pigmentation, HIV

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

INTRODUCTION

Oral lesions are not only indicators but can also be predictors for the progression of the disease,as well as its response to treatment. Oral health mirrors our overall health.Many systemic disorders affecting the individuals are reflected through oral health.One such disease being HIV/AIDS.[1]

In 70-90% of HIV-positive patients oral lesions are observed during the different stages of the disease which includes lesions like oral candidiasis, hairy leukoplakia, Kaposi sarcoma, linear gingival erythema, necrotizing ulcerative periodontitis, aphthous ulcer, human papillomavirus infection, hyperpigmentation, oral submucous fibrosis, xerostomia, leukoplakia, herpes zoster, non-Hodgkin's lymphoma, histoplasmosis, carcinoma, penicilliosis marneffei, exfoliative cheilitis, HIV salivary gland disease, perioral molluscum contagiosum, staphylococcus aureus infections, and petechiae. One of these oral manifestationis hyperpigmentation.[2]

Drugsoften considered to be implicated in the development of oral melanin hyperpigmentation are quinacrine, chloroquine, hydroxychloroquine (antimalarial), anti-retro viral therapy (antiviral), minocycline (tetracycline-antibacterial), oral contraceptives, phenolphthalein (laxative), clofazimine (anti-leprosy), ketoconazole (antifungal), amiodarone, nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, psychotropic drugs.Adverse

©2023Int. J. LifeSci.Biotechnol.Pharma.Res.

drug reactions, drug toxicities and drug interactions are an important challenge seen with highly active antiretroviral treatment (HAART) and antitubercular treatment.[3,4]

Tenofovir, is oneoftheantiretroviral treatment regimen used tomanageHIV. The pathogenesis of drug induced pigmentation and their clinical pattern vary according to the causative drug. Hyperpigmentation is usually secondary to an increase in melanin due to:

A. The stimulation of melanocytes.
B. A pigmentary incontinence developed after an unspecified cutaneous inflammation.

It can also be secondary to the accumulation of the drug or its metabolites in the dermis forming complexes with melanin or iron.Microscopically,basilar melanosis without melanocytic proliferation is noted in drug induced melanosis.[1]

In the present study, we assessed the prevalence of Tenofovir-induced hyper pigmentation among HIV-infected patientsin Kodagu Karnataka.

METHODS

A cross sectional study was conducted on a cohort of168 HIV-seropositive patientstakingTenofovir regimen,attending the ICTC centre at Kodagu.The study was done by dental departmentafter obtaining the Institutional Ethical Committee clearance (KOIMS/IEC/05/2018-19).

The HIV status of all the subjects who had previously been established by two enzyme-linked immunosorbent assays (ELISA-HIV) were included in the study. The study was conducted over a period of 6 months.

Participants were given both verbal and written information in their mother tongues about the nature of the studyand written informed consent was obtained. All personal information about the patients were kept confidential.

Oral physician examined and interviewed all the subjects, recorded the relevant clinical data, and consulted the medical records for supplementary medical history.

The collected data comprised of age, gender, CD4+ T cell count, history of systemic disease, drug history,site affected both intra oral and extra oral according to WHO criteria.

Chi squaretest was used to assess the relationship between categorical variables. 5% significance level was used.

RESULTS

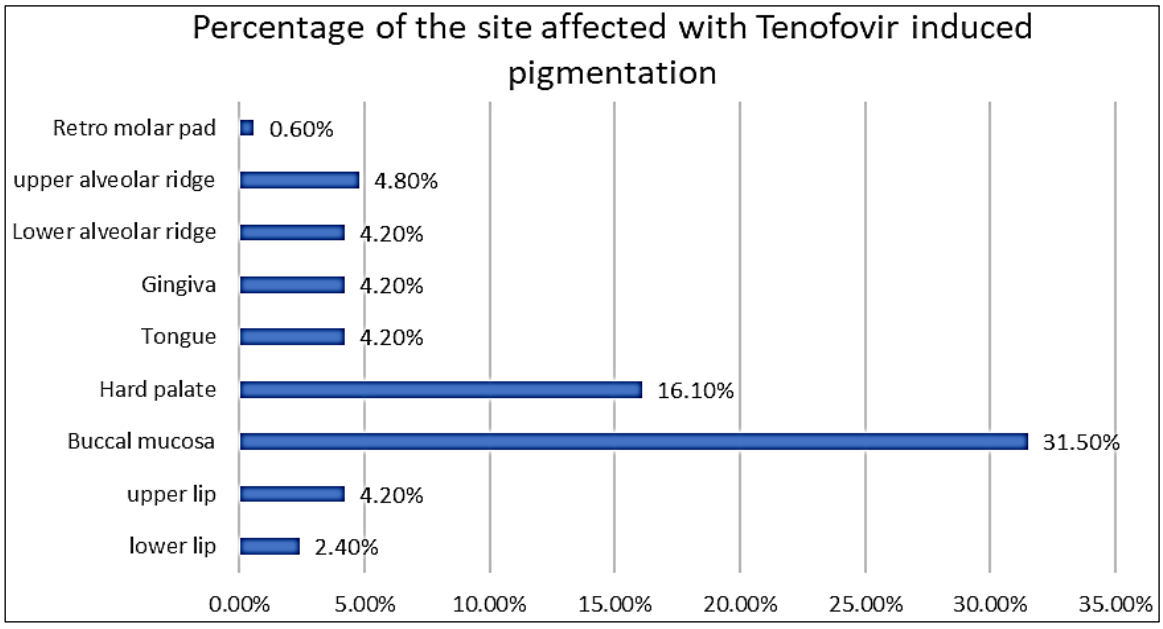


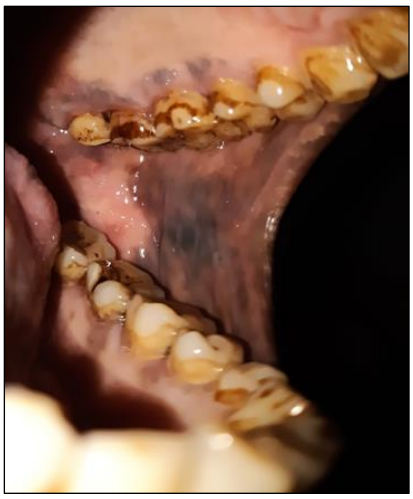
Fig 1: Intra oral siteswith pigmentation in patients on Tenofovir

A total of 168 subjects who were on Tenofovirwere included in the study. Oral mucosal pigmentation was seen in 52 (31%) and 6 (3.6%) subjects had both intra oral and extra oral pigmentation i.e. pigmentation of skin, nail and oral cavity was noted.

In our study the most commonly involved intra oral sites was buccal mucosa 53(31.5%) followed byhard palate 27(16.1%),upper alveolar ridge 8 (4.8 %),tongue 7(4.2%),gingiva 7 (4.2%),lower alveolar ridge 7 (4.2%), upper lip 7(4.2%), lower lip 4(2.4%), retromolar area 1 (0.6%).{figure 1} Patients were able to appreciate the discolorationin more visible areas like buccal mucosa,hard palate and tongueand reported that pigmentationsucceed with the initiation of highly active anti-retroviral therapy. No previous

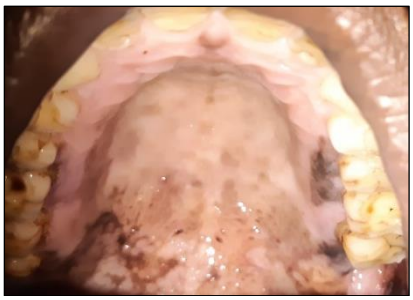
©2023Int. J. LifeSci.Biotechnol.Pharma.Res.

studies havedocumentedoral hyperpigmentationinadult HIV patients on Tenofovir.
Asymptomatic,multiple, discrete, macularbrownish-black discolouration of the oral mucosa was the characteristic feature of Tenofovir induced pigmentation in people who were followingHAART regimenin our study. {Picture 1-5} Similarly asymptomatic, greyish-black discoloration of the tongue was o bserved in few individuals with no toxicityin those who were on Zidovudine in previous studies[5].
In 6 (3.6%) subjects pigmentationalong the face and nails was seenin our study who were on Tenofovir therapy. (Picture 6,7) One case of mucocutaneous hyperpigmentation secondary to tenofovir had reported that striated melanonychia may or may not be associated with diffuse hyperpigmentation of the skin and mucous membranes.[6] Longitudinal melanonychia(Picture 7)was seen in our patients similar to thestudies which were reported in Zidovudine induced pigmentation.[7] This pigmentation must be distinguished from the brownish hyperpigmented stripes that are seen in HIV patients who are not on any drugs. Since it is a clinical diagnosis it should be confirmed by histopathology in further studies.
The mean age of the group of individuals who were on Tenofovirwith no pigmentation was 38.3 years,whereas the mean age of the group of individuals with pigmentationusing Tenofovir was 36.3 years. There was no significant difference in the mean age or in the age categories between the no drug inducedpigmentation group and the one with pigmentation.
Out of 168HIV-seropositive subjects on tenofovir regimen, 87 females and 81 males, were included in this study (F : M = 0.89).
Thegroup on Tenofovir with no hyperpigmentationcomprised F : M = 3.5 : 1 whereas the groupwith pigmentation on TenofovircomprisedF : M = 1.31 : 1.Similar to another study population with 16 patients (1.31%) diagnosed as drug-induced hyperpigmentation with 50%male and the mean age was 63years, standard deviation 16 years; range, 34 to 86 years similar to our study.[2]
Out of the 168 patients on Tenofovir having pigmentation43 (64.2%)had low immunity (CD4 < 500) while 24(35.8%) patients had CD4 >500. It has also been reported that at the time of the studies, the frequency of drug induced hyperpigmentation was inversely proportional to the CD4+ T cell count.
Out of 168 patients on Tenofovirtherapy34 people (50.8%) were onTenofovir regimen for more than 5years and 33 people (49.3%) were on Tenofovir therapy for less than 5 years. Previous studies have documented that the drug Zidovudine/azidothymidine hasbeen reportedto induce melanin hyperpigmentation within a month of initiating treatment.[8, 9]
In our study there was no significant association betweenage, gender and the presence or absence of oral pigmentation in those who were on Tenofovir.
However, differentiation between drug induced pigmentation (Tenofovir) and HIV oral mucosal hyperpigmentation relies on self-reported histories given by the patients that are not always reliable. Since oral pigmentation is asymptomatic and sometimes theaffected oral sites are not readily visible to the individuals, a largenumber of subjects couldn’tstate with confidence whether or not they had pigmentationbefore or after the start of the drug Tenofovir. Further confirmation of the lesion using histopathological examination was not done since the lesions were asymptomatic and conducting an invasive procedure like biopsy to acertain was unethical. Further studies are required to correlate the findings with histopathological examination of the affected sites to check for the presence of drug metabolites in the mucosa.

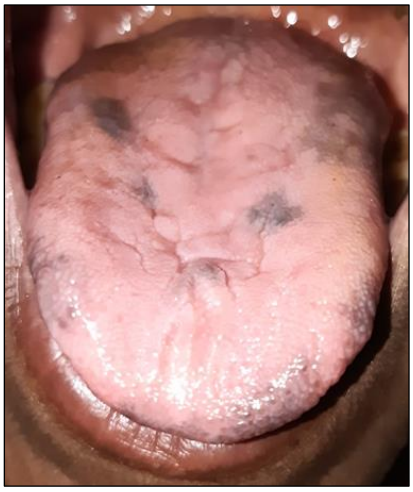


Picture 1: Discrete pigmentation along the palate andbluish black diffuse pigmentation along left buccal mucosa

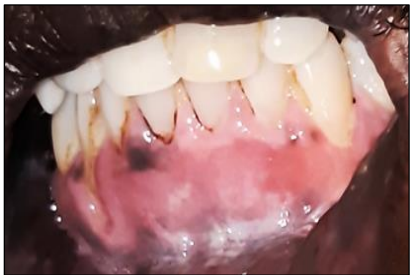
©2023Int. J. LifeSci.Biotechnol.Pharma.Res.



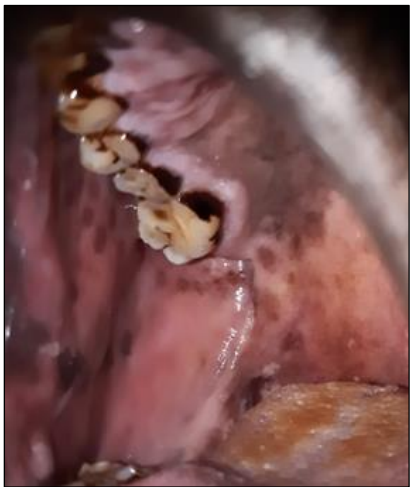
Picture 2: Multiple discretebrownishblack pigmentation along the palate



Picture 3: Multiple discretebluish black pigmentation along the tongue



Picture 4: Discrete bluish black pigmentation of lower attached gingiva



Picture 5: Discrete pigmentation along the palate and brownish black pigmentation along right buccal mucosa

©2023Int. J. LifeSci.Biotechnol.Pharma.Res.

Picture 6: Discrete pigmentation seen on the face

Picture 7: Longitudnal melanochia noted on the nails on patients taking Tenofovir therapy

DISCUSSION

To the best of our knowledge there is no other studiesdocumenting Tenofavir induced oralhyperpigmentation in HIV patients on Anti-retroviral therapy.

The prevalence of drug induced oral pigmentation (Tenofavir) in our study had31.1% intraoral pigmentation, 3% extra oral pigmentationsignificantly higher than the other reported studies from other countries in which drug-induced hyperpigmentation was estimated to account for 10% to 20% [1],Sub-Saharan Africa (Tanzania 4.7%, Kenya 6%) [10,11]in Europe (Italy 6.4%, Greece 2%),in Venezuela (38%) [12] but similar to the study conducted inIndia (26% to 35%)[13-16] in which general oral mucosal pigmentation was documented and not preferentially Tenofavir induced oral pigmentation among HIV patients receiving highly active anti-retroviral therapy.[5]This increase inthe prevalence could be due to documentation that is done on south Indian population of Kodagu comprising largely persons of Asian and mixed racial/ethnic descent.

Oral pigmentation is found to be common in dark skinned patients in previous studies who were on Zidovuidine and it seems to be reversible. This pigmentation also could be due to the upregulation of IL-1, IL-6, and TNF-α associated with HIV infection triggers keratinocytes and melanocytes to produce alpha melanocyte stimulating hormone (αMSH) which has the capacity to stimulate melanogenesis, resulting in increased production of melanin, manifesting clinically as oral pigmentation.[17]

The oral pigmentation may be drug induced, a consequence of adrenal insufficiency or idiopathic. In HIV-seropositive subjects, oral mucosal hyperpigmentationmay also be induced by HIV-associated systemic conditions. Evidences have shown that the prevalence of oral pigmentationis higher in HIV-seropositive subjects on HAART than in HIV-seropositive patients who haven't started HAART.[4,10,17]hence histopathological evaluation is recommended in further studies.

In a study conducted at dermatology clinicson various drug therapies at Rio Hortega university for a sample size of 1217 patients between August 1, 2017 to April 20, 2018,16 patients (1.31%) were diagnosed of drug induced hyperpigmentation in whom theynoted hyperpigmentation of the oral mucosa in 4 patients,hyperpigmentation ofphotograph-exposed areas in 6,4 people had labial hyperpigmentation similar to our study andnail hyperpigmentation in 1 patient[3].

A study on minocycline had noted hyperpigmentation of the oral mucosa in 4 patients. The papillary gums were the most frequently affected, followed by the marginal gingiva and the buccal mucosa. Thoughnot a

©2023Int. J. LifeSci.Biotechnol.Pharma.Res.

medical problem patients have complained about the blackish color of their gums. Oral pigmentation caused by drugs occurs equally in all races and without differences in sex.[18] which is similar to our study.

Labial hyperpigmentation is associated with a wide variety of conditions.The drugs most associated with labial hyperpigmentation are minocycline, zidovudine, cyclophosphamide, doxorubicin, citalopram, levodopa, nicotine, and tacrolimus.In addition to drugs genodermatosis, inflammatory diseases,endocrine disordersand neoplasms are associated with labial hyperpigmentation. Drugs that cause labial hyperpigmentation are also associated with hyperpigmentation in other areas, such as the oral mucosa, skin, and nails.[2,4]

Intraoral slate gray pigmentation was noted among those onantimalarials such as quinacrine, chloroquine, and hydroxychloroquine. Tetracyclines cause pigmentation of the teeth and bones, minocycline causes brownish pigmentation of soft tissues such ason the hard palate, gums, mucosa, and the tongue.[1,19,20]

Several cases have reported hyperpigmentation of the oral mucosa due to hydroxychloroquine. There are also cases of hyperpigmentation of the nails or nose due to quinacrine or quinidine[21].

CONCLUSION

Hyperpigmentation is one of themajor side effect with prolonged use of anti-retro viral therapy like Tenofovir. It is unresearched and unknown whether or not Tenofovirinduced oral pigmentation has any pathological significance.

Further studies are required to see if Tenofovir pigmentation has any effect on the oral health and the quality of life among the patients who are on highly active antiretroviral therapy.

REFERENCES

1. Alawi F. Pigmented lesions of the oral cavity: an update. Dent Clin North Am. 2013 Oct;57(4):699-710.
2. Berberi A, Aoun G. Oral lesions associated with human immunodeficiency virus in 75 adult patients: a clinical study. J Korean Assoc Oral Maxillofac Surg. 2017 Dec;43(6):388-394.
3. Giménez García RM, Carrasco Molina S. Drug-Induced Hyperpigmentation: Review and Case Series. J Am Board Fam Med. 2019 Jul-Aug;32(4):628-638.
4. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. Am J Clin Dermatol. 2001;2(4):253-62.
5. Filitis DC, Graber EM. Minocycline-induced hyperpigmentation involving the oral mucosa after short-term minocycline use. Cutis. 2013 Jul;92(1):46-8.
6. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. Indian Dermatol Online J. 2014 Jan;5(1):98-9.
7. Rosebush MS, Briody AN, Cordell KG. Black and Brown: Non-neoplastic Pigmentation of the Oral Mucosa. Head Neck Pathol. 2019 Mar;13(1):47-55.
8. Sreeja C, Ramakrishnan K, Vijayalakshmi D, Devi M, Aesha I, Vijayabanu B. Oral pigmentation: A review. J Pharm Bioallied Sci. 2015 Aug;7(Suppl 2)
9. Capelli L, Garuti RA, Carmona Cuello LE, Sanz A, Oborski MR, León SA, *et al*. Hiperpigmentación cutáneo-mucosa y ungular secundaria a tenofovir. Arch Argent Dermatol [Internet]. 2013 [cited 2023 Jan 29];23–6.
10. Singal A, Bisherwal K. Melanonychia: Etiology, Diagnosis, and Treatment. Indian Dermatol Online J. 2020 Jan 13;11(1):1-11.
11. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf. 2002;25(5):345-72.
12. Chawre SM, Pore SM, Nandeshwar MB, Masood NM. Zidovudine-induced nail pigmentation in a 12-year-old boy. Indian J Pharmacol. 2012 Nov-Dec;44(6):801-2.
13. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. Indian Dermatol Online J. 2014 Jan;5(1):98-9.
14. Chandran R, Feller L, Lemmer J, Khammissa RAG. HIV-Associated Oral Mucosal Melanin Hyperpigmentation: A Clinical Study in a South African Population Sample. AIDS Res Treat [Internet]. 2016 [cited 2022 Feb 2];2016:8389214.
15. Hamza OJM, Matee MIN, Simon ENM, Kikwilu E, Moshi MJ, Mugusi F, *et al*. Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy [HAART] in Dar es Salaam, Tanzania. BMC Oral Health. 2006 Aug 18;6:12.
16. Butt FM, Chindia ML, Vaghela VP, Mandalia K. Oral manifestations of HIV/AIDS in a Kenyan provincial hospital. East Afr Med J. 2001 Aug;78(8):398-401.
17. Bravo IM, Correnti M, Escalona L, Perrone M, Brito A, Tovar V, *et al*. Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. Med Oral Patol Oral Cirugia Bucal. 2006 Jan 1;11(1):E33-39.
18. Ranganathan K, Umadevi M, Saraswathi TR, Kumarasamy N, Solomon S, Johnson N. Oral lesions and conditions associated with human immunodeficiency virus infection in 1000 South Indian patients. Ann Acad Med Singapore. 2004 Jul;33(4 Suppl):37–42.
19. Ranganathan K, Reddy BV, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral

©2023Int. J. LifeSci.Biotechnol.Pharma.Res.

lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. Oral Dis. 2000 May;6(3):152–7.
20. Sharma G, Pai KM, Suhas S, Ramapuram JT, Doshi D, Anup N. Oral manifestations in HIV/AIDS infected patients from India. Oral Dis. 2006 Nov;12(6):537–42.
21. Hassan S, Zhou XA. Drug Induced Pigmentation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Jan 29].

©2023Int. J. LifeSci.Biotechnol.Pharma.Res.